Potassium Permanganate: What is it and how can we ensure it is safely used in US Aquaculture

Problem Statement

Potassium permanganate (PP) is an enigmatic chemical as used in domestic aquaculture. Globally, PP is commonly used in potable water to oxidize iron and manganese, taste and odor compounds, and nuisance organisms, and to control disinfection by-products (EPA 1999). In aquaculture and fisheries management it has been used to increase dissolved oxygen in fish rearing ponds (Mathis et al. 1962), to generally oxidize organic matter (Engstrom-Heg 1971; Jee and Plumb 1981), remove off-flavor compounds or as an algaecide (Haney 1964), inactivate the piscicides actinomycin-A and rotenone (Lawrence 1956; Berger et al. 1969), and therapeutically to control mortality caused by bacterial gill disease(s), external columnaris, and external parasite or external fungal infestations (Hoffman 1969; Hoffman 1965; Davis 1923). In 1986, the Arkansas Cooperative Extension Service (Schnick, Meyer and Gray 1986) identified PP as a "registered or approved water treatment compound for aquatic or fishery use." They further state that EPA exempted PP from registration. Claims to the therapeutic efficacy of PP are anecdotal (e.g. Kingsbury, O.R. and G.C. Embody 1932) and its therapeutic attributes have proved difficult to demonstrate under controlled conditions (e.g. Tieman and Goodwin 2001; Darwish et al. 2008).

In the early 1990's, the U.S. Food and Drug Administration (FDA) and the aquaculture community recognized that all entities would benefit from a concerted effort to obtain drug approvals for several of the drugs and/or chemicals then in use. It was recognized that some of these chemicals were really pesticides and should be labeled as pesticides, while some were clearly used as drugs and should ultimately be approved and labeled as a drug. In the early 1990's there was a rush to identify compounds that needed to be approved by federal authorities. It was at that time that compounds such as sodium chloride and oxygen were identified as subject to drug approval by FDA. In 1992, the American Fisheries Society, Fish Health Section petitioned the FDA's Center for Veterinary Medicine (CVM) to "exempt from regulatory action" various drugs or chemicals, including PP. Hence was spawned the CVM Low Regulatory Priority (LRP) list. Although PP was proposed for inclusion on the LRP list CVM elected to defer such a regulatory decision, and instead termed it to be a compound of "deferred regulatory status" (i.e., "…at this time we choose not to regulate"). It is unclear exactly when PP became of interest as a candidate drug for potential FDA-approval, but it now appears on several lists delineating aquaculture drug approval priorities (e.g. US Dept. Interior 2001). Now, almost 20 years later, efforts towards approval of PP as a drug have languished. Some work has been done to determine if there are manganese residues in PP treated fish (there are none), what acute toxicity may be (Hobbs et al. 2006) and efforts have been made to demonstrate therapeutic efficacy (e.g. Darwish et al. 2008). To date, demonstration of PP induced reduction in water column bacterial loads has occurred but demonstration of the efficacy of PP as a therapeutic agent has proved illusive (Tieman and Goodwin 2001).

The broad use patterns of PP yet difficulty establishing therapeutic value under controlled conditions attest to its enigmatic properties. Carus Chemical, the sole US manufacturer of PP, did not elect to renew their EPA labels as a pesticide (for the control of zebra mussels; CAIROX® ZM) or algaecide (CAIROX® Algicide) because such labeling was not needed for its real uses. PP is an oxidizer of things organic and indeed any value of PP to aquaculturists and fisheries manager's results from its general oxidizing action rather than any specific targeted drug or pesticide properties.

The characteristics of PP and its historical use patterns in aquaculture raise several important questions.

1. What are the actual uses of PP in domestic aquaculture and fisheries and what would any sponsor want to claim on a label?
2. What is its mechanism of action?
3. Is PP really a therapeutic drug, a pesticide or something different?
4. If PP is not a therapeutic drug and it is not a pesticide, what is it and how can we ensure it is used safely for its intended purpose and in a manner that protects public health?
5. Are there other drug classifications that might apply and if so, what are the approval requirements?

Uses in Domestic Aquaculture and Fisheries

While there is not a published, systematic review of how PP is commonly used in aquaculture, experience by several aquaculturists, fish health managers and fisheries managers identify the following:

1. PP is no longer used to generate oxygen in ponds. The amount of oxygen chemically released from a PP application is barely measureable and only transient. In ponds the presence of high organic matter loads, either in the sediments or suspended in the water column, make dosaging for significant oxygen availability problematic (note: the same would be true for therapeutic treatment). There are now more economical and efficient mechanical methods to add oxygen to ponds. It probably was never used to provide oxygen in serial flow-through systems because of the design of these types of operations.

2. PP is used to help reduce organic loads in serial flow-through raceway systems and perhaps in ponds. Empirical evidence indicates it enhances fish survivability

(e.g. trout) and improves feed conversion efficiency. The mechanism for enhanced survivability may be its oxidation of organic matter including reduction in water column bacterial loads. Anecdotal information suggests fish reared in water heavily laden with organic matter may not experience the benefits of PP use.

3. PP is no longer used in channel catfish or other warm water aquaculture ponds in an effort to control the production of off-flavor compounds. PP is difficult to apply in ponds, is expensive, and there is so much organic matter in a pond that continuous exposure to active PP would probably be required to control off-flavor.

4. If PP is used as an algaecide, it is rare. There are more effective chemicals (e.g. chelated copper or copper sulfate) for this purpose. PP might be used in soft water where copper toxicity would be increased.

5. PP is used by fishery biologists and aquaculturists to inactivate actinomycin-A and rotenone in ponds and flowing waters. Actinomycin is a selective piscicide directed against scaled fishes and rotenone is a broad spectrum fish toxicant.

6. PP is used to treat ponds of catfish showing signs of external columnaris (gills and skin). Its efficacy has never been scientifically demonstrated. In flow through systems with relatively low organic loads, empirical evidence indicates it reduces the prevalence of environmental or bacterial gill disease. It may be effective to treat eggs infested with *Saprolegnia* spp., but this has not been systematically evaluated. Its effectiveness to treat infestations of *Ichthyopthirius* or other external parasitic infestations in actual production environments is assumed but has not been critically evaluated. The EPA (1999) could not identify any scientific literature that demonstrated the efficacy of PP to inactivate protozoans.

7. It has been suggested that PP is more of a disinfectant than a disease treatment. Empirical evidence under actual aquaculture conditions supports this concept. The disinfectant properties of PP have been reviewed by EPA (1999). Dosage of 2-4 mg/L can be effective at killing bacteria if the exposure is long enough. Efficacy against viruses has been documented at shorter exposure times (10 min.) if a greater dosage (e.g. 50 mg/L) is applied. Practical experience in aquaculture suggests freshwater fish will tolerate a dose of 1-2 mg/L during a 20 – 60 min exposure when organic load is low.

Mechanism of Action

The EPA (1999) states that PP "is highly reactive under conditions found in the water industry." The EPA does not define what the conditions are in the water industry. They further state that PP will oxidize a wide variety of inorganic and organic substances and that all reactions are exothermic. PP (Mn 7+) is reduced to manganese dioxide (MnO_2) + (Mn 4+) which precipitates out of solution (Hazen and Sawyer 1992). Reaction rates for the oxidation of constituents found in natural waters are relatively fast and depend on temperature, pH, and dosage. Under acidic conditions the oxidation half-reactions are (CRC 1990):

$$MnO_4^{-} + 4H^{+} + 3e^{-} \rightarrow MnO_2 + 2H_2O$$

$$MnO_4^{-} + 8H^{+} + 5e^{-} \rightarrow Mn^{2+} + 4H_2O$$

Under alkaline conditions, the oxidation half-reaction is (CRC 1990):

$$MnO_4^{-} + 2H_2O + 3e^{-} \rightarrow MnO_2 + 4OH^{-}$$

In water used for freshwater aquaculture, the reactions would be the same. However, in contrast to drinking water, the water used for aquaculture would generally contain significant loads of organic matter. This is a significant issue because the organic load in the water column or in sediments will affect the impact a particular PP dose will have on any specific, anticipated outcome. The presence of oxidizable organics or inorganics in the water reduces the disinfection effectiveness of PP because some of the applied PP will be consumed in the oxidation of organics and inorganics (EPA 1999). This probably accounts for the wide dosage requests FDA CVM has undoubtedly received in their consideration of PP as a drug. This would also account for the wide variation in fish tolerance to PP reported by fishery biologists.

Empiric observations suggest that under low organic loading conditions, rainbow trout appear to well tolerate 1-2 mg/L concentrations when exposures last 20-30 minutes.

Drug or Pesticide?

By Federal Food Drug and Cosmetic Act definition, the term "drug" means (A) articles recognized in the official United States Pharmacopoeia, official Homoeopathic Pharmacopoeia of the United States, or official National Formulary, or any supplement to any of them; and (B) articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; and (C) articles (other than food) intended to affect the structure or any function of the body of man or other animals; and (D) articles intended for use as a component of any article specified in clause (A), (B), or (C). A food or dietary supplement for which a claim, subject to sections 403(r)(1)(B) and 403(r)(3) or sections 403(r)(1)(B) and 403(r)(5)(D), is made in accordance with the requirements of section 403(r) is not a drug solely because the label or the labeling contains such a claim. A food, dietary ingredient, or dietary supplement for which a truthful and not misleading statement is made in accordance with section 403(r)(6) is not a drug under clause (C) solely because the label or the labeling contains such a statement.

Arguably, while some aquaculturists may intend PP to act as drug, there is in fact no evidence it is effective as a therapeutic drug. Controlled clinical trials fail to demonstrate its efficacy to treat external columnaris disease or infestations of *Ichthyopthirius* (Darwish et al. 2008). Its efficacy to treat bacterial gill disease (BGD) is also suspect because of the nature of BGD. BGD is associated with a variety of opportunistic pathogens or bacteria in the water column including aeromonads, flavobacteria and pseudomonad's. The disease itself is variously described as environmental gill disease reflecting the importance of poor environmental conditions in its occurrence. Claims of BGD treatment success may simply reflect improvement in environmental conditions associated with the impact of a suitable oxidizing agent.

Should PP be considered a pesticide? The Federal Insecticide, Fungicide and Rodenticide Act (FIFRA) defines the term "pesticide" to mean:

(1) any substance or mixture of substances intended for preventing, destroying, repelling, or mitigating any pest,

(2) any substance or mixture of substances intended for use as a plant regulator, defoliant, or desiccant, and

(3) any nitrogen stabilizer, except that the term "pesticide" shall not include any article that is a "new animal drug" within the meaning of section 321 (w) of title 21, that has been determined by the Secretary of Health and Human Services not to be a new animal drug by a regulation establishing conditions of use for the article, or that is an animal feed within the meaning of section 321 (x) of title 21 bearing or containing a new animal drug. The term "pesticide" does not include liquid chemical sterilant products (including any sterilant or subordinate disinfectant claims on such products) for use on a critical or semi-critical device, as defined in section 321 of title 21. For purposes of the preceding sentence, the term "critical device" includes any device which is introduced directly into the human body, either into or in contact with the bloodstream or normally sterile areas of the body and the term "semi-critical device" includes any device which contacts intact mucous membranes but which does not ordinarily penetrate the blood barrier or otherwise enter normally sterile areas of the body."

PP does not satisfy the above-described definition since there is not a specific pest the chemical is intended to eliminate.

The enigmatic nature of potassium permanganate seems clear. PP is neither a drug nor a pesticide. It is an oxidizer of organic matter and should be treated as such.

Food Animal and Environmental Safety Issues

Potassium permanganate does appear to have oxidizing properties that are useful in domestic aquaculture. Jurisdictional issues arise (should it be regulated as a drug, pesticide, or exempt from regulation when used as an oxidizer?) because of its enigmatic character. Demonstration of its efficacy as a therapeutic drug has been problematic. Carus Chemical historically held labels for PP as a pesticide for zebra mussels and as an algaecide. These labels have since lapsed with no interest in approval renewals.

In the interim, question arises as to target animal safety, residues, and environmental impact. Some information is already available on these issues.

1. Over time, the tolerance of various fishes to PP exposure has been empirically determined. In flow through, serial reuse rainbow trout aquaculture, a dose of 1-2 mg/L for 20-30 minutes is well tolerated. Organic loading characteristics in these environments have not been systematically determined but appear to be relatively consistent since repeated exposure to PP does not adversely impact the fish. Indeed, repeated exposure to PP appears to enhance fish survivability at least under intensive farming conditions. Channel catfish exposed to PP have a more varied history of impact. Current recommendation is that the permanganate demand be determined before channel catfish in a pond are exposed to PP (Tucker 1989). Low permanganate demand necessitates a reduced PP dosage (1-2 mg/L). Thus, target animal safety has been empirically determined.

2. Two residue studies we are familiar with have been conducted. Griffin (1994) exposed channel catfish to various amounts of PP over an extended time period. Manganese concentrations in filet muscle and liver tissue were examined. No difference was detected between exposed and control catfish. We understand that study has been submitted to the FDA CVM.

A second study (unpublished, Clear Springs Foods conducted in association with B. Griffin), this one on rainbow trout fingerlings, has been conducted. Rainbow trout were repetitively exposed by 20 minute bath exposure to PP two times per week for nine months. Manganese concentrations in filet muscle and liver tissue were examined. No difference was detected between exposed and un-exposed rainbow trout.

We conclude from these two studies that manganese residues in fish occurring as a result of PP bath exposure do not occur.

3. Environmental impacts are largely unknown. In channel catfish and rainbow trout ponds water is not generally discharged. Permanganate activity is transitory because of organic matter content in the ponds so it is possible that there is no impact on public waters as a consequence of PP use in aquaculture (e.g. Hobbs et al. 2006). The impact of PP use from serial re-use systems that discharge to public waters is of unknown consequence although dilution from other non-treated raceways would likely eliminate potential impact. Under practical aquaculture conditions, the duration of oxidizing

activity of PP is dependent on organic loads (Tucker and Robinson 1990). These will be highly variable depending on location. The presence of a pink color is used to indicate residual oxidizing capacity. For locations where discharge of residual oxidization potential is an issue, a program could be designed to ensure no pink colored water is discharged. This could occur via reducing the number of raceways treated at a time. The remaining potential environmental issue is discharge of manganese. There are no federal limits or water quality standards for Mn identified in the Code of Federal Regulations. Individual states may have defined standards. In the absence of standards, the default standard would be background concentrations. Some effort could be devoted to determine background levels on a case-by-case basis to ensure use would be in compliance with this default standard.

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